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THE MEASUREMENT OF CAPILLARY PERMEABILITY CHANGES IN THE IRRADIATED RAT USING A DOUBLE ISOTOPE TECHNIQUE

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

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THE MEASUREMENT OF CAPILLARY PERMEABILITY CHANGES IN THE IRRADIATED RAT USING A DOUBLE ISOTOPE TECHNIQUE

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FOREWORD
(Nontechnical summary)

Changes in capillary permeability shortly after irradiation are of interest because of the possible connection with radiation-induced incapacitation and with the generalized capillary fragility that may occur several days after irradiation.

A new technique using two types of radioactively labeled albumin was developed to measure capillary permeability in the small intestine and in skeletal muscle of the rat at various times after irradiation.

It was found that in rat small intestine there was an increase in capillary permeability immediately after 10,000 rads ^{60}Co irradiation that could be completely abolished if the drug cyproheptadine was injected 30 minutes prior to irradiation. This drug is a powerful antagonist of histamine and serotonin, two substances that are known to increase capillary permeability and to dilate blood vessels. These results indicate that histamine or serotonin may be responsible for the initial increase in capillary permeability.

In rats exposed to 800 rads of 30 MeV electrons (LINAC) there was an initial increase in permeability followed by a return to normal levels. A second increase was measured beginning at 8 hours and leveling off at 24 hours. Thereafter the permeability remained relatively constant for several days and was not susceptible to treatment with cyproheptadine as measured 48 hours postirradiation. This indicates that the secondary increase is not due to histamine or serotonin. It may be due to structural defects that may lead to internal bleeding.

ABSTRACT

Capillary permeability was measured using ^{131}I albumin and ^{125}I albumin to assay the movement of albumin out of the bloodstream into the interstitial fluid of small intestine and muscle of the irradiated rat. One hour after 800 rads 30 MeV electron whole-body irradiation, small intestine capillary permeability increased significantly, returned to normal levels in a few hours, and then after 8 hours increased and remained at 65 percent above control levels for several days. Muscle capillary permeability increased within 2 hours after irradiation and remained elevated for several days. Cyproheptadine, an antiserotonin-antihistamine, completely blocked a 45 percent increase in small intestine capillary permeability seen immediately after 10,000 rads ^{60}Co irradiation but had little effect at 48 hours after irradiation.

I. INTRODUCTION

Capillary permeability in the rat increases immediately following midlethal whole-body ionizing irradiation, returns to normal levels within a few hours, and then increases and remains elevated for several days.[3] As has been reported, the initial changes might be due to the liberation of serotonin[15] and histamine[3,5,8,15] from mast cells immediately following irradiation. The late changes could be the manifestation of structural defects in the capillary endothelium several days later. Since both serotonin and histamine have been considered as the agents responsible for the early changes in capillary permeability, it is possible that a drug which blocks the action of both serotonin and histamine could be particularly effective in abolishing the increase in capillary permeability immediately after irradiation. This was tested, using a double isotope technique to measure the movement of albumin out of the bloodstream into the interstitial fluid of the small intestine in the presence and absence of an antiserotonin-antihistamine drug.

II. METHODS AND MATERIALS

Animals. Male Sprague-Dawley rats individually housed in wire mesh cages and weighing 280-350 g were used in this study. These rats were allowed free access to food and water.

Isotopically labeled albumin. 1 mCi ^{131}I human serum albumin (Albumotope I 131, E. R. Squibb) in a volume of 2 ml was dialyzed at 4°C against 1 liter 0.9 percent NaCl for 24 hours; and 0.25 mCi ^{125}I human serum albumin (Albumotope I 125, E. R. Squibb) in a volume of 5 ml was also dialyzed at 4°C against 1 liter 0.9 percent NaCl for 24 hours.

After such dialysis, less than 1 percent of the radioactive iodine remained in solution when assayed by the precipitation of the protein by cold 10 percent trichloroacetic acid.[3]

In preliminary experiments, undialyzed albumin was injected into a rat and after 1 hour the rat was bled and the plasma was used. Since the results with that plasma were similar to the results with the dialyzed albumin, the latter was used in the subsequent work reported here. Both albumins were diluted with 0.9 percent NaCl to about 20 μCi/ml for injection.

Antiserotonin-antihistamine. In some experiments, 0.1 mg/kg of cyproheptadine was given subcutaneously 30 minutes prior to the injection of ^{131}I albumin.

Irradiation. In the first experiment the rats were irradiated in groups of six by a water-scattered 30 MeV linear accelerator (LINAC) electron beam. The dose was delivered in 4-μsec pulses, 40 rads per pulse, 20 pulses in 20 seconds for a total whole-body dose of 800 rads $\pm$ 7 percent. It was measured with thermoluminescent dosimeters calibrated with cobalt-60.

For technical reasons the LINAC was unavailable, and therefore in the second experiment the rats were irradiated with a bilateral ^{60}Co source. A larger dose was chosen to assure a maximal change in capillary permeability. The rats received 10,000 rads $\pm$ 5 percent whole-body irradiation at 900 rads/minute.

The relative biological effectiveness for fast electrons to ^{60}Co gamma rays has been shown to be about 1 for a variety of systems including cultured mammalian cells[12] and mouse lethality.[9] Therefore, the results from the two sources should be comparable.

Experimental procedure. The rats were anesthetized with 6 mg Nembutal/100 g intraperitoneally. A polyethylene PE-50 cannula was inserted into the right jugular vein for injection of the isotopes and withdrawal of blood. First, about 1 μCi of ^{131}I albumin was injected. This was followed 20 minutes later with an injection of about 1 μCi of ^{125}I albumin. Each injection was washed in with about 0.1 ml physiological saline. About 10 ml of blood were withdrawn into a heparinized syringe via the cannula 30 minutes after the ^{131}I albumin injection, following which the animal was sacrificed by creating a pneumothorax. The blood was then centrifuged and a 1-ml plasma sample was placed in a vial.

A sample of small intestine including most of the jejunum and part of the ileum was removed. The mesentery was stripped from the sample and the contents expressed. Part of the abdominal wall and the gluteus maximus from one leg were also taken as muscle samples. All samples were weighed wet and then digested with 3 M KOH at 60^{o}C overnight. The ^{125}I and ^{131}I radioactivity of each sample was measured with a dual channel scintillation counter. The resulting data were used to calculate the capillary permeability surface area product (PS) per gram of tissue for each tissue sample (see section III. Theory).

PS, as used by Garlick and Renkin,[1] is defined by Fick's law: $F = PS \cdot \Delta C$ where F is the flux of a solute through a membrane and ΔC is the concentration difference across the membrane for that solute.

The term capillary permeability has frequently been used in the literature to mean capillary PS as just defined. For the sake of brevity, capillary permeability is

used occasionally in this paper but should always be taken to mean the capillary permeability surface area product.

In the first experiment, using the LINAC, the experimental procedure was conducted on groups of rats at various times after irradiation to follow the changes in capillary PS.

In the second experiment, using ^{60}Co irradiation, the procedure was conducted immediately after irradiation (0-time group) and 48 hours later. Half of the 0-time group received 0.1 mg/kg of cyproheptadine subcutaneously 30 minutes before irradiation. Just before irradiation, all the animals in the group were injected with ^{131}I albumin and then irradiated. Irradiation took about 11 minutes, leaving adequate time to complete the rest of the procedure.

Half of the 48-hour group received 0.1 mg/kg of cyproheptadine 30 minutes prior to the injection of ^{131}I albumin.

Statistical analysis. The Mann-Whitney U test[11] was used throughout to evaluate the statistical significance of the differences between groups. Significance was assigned at the 5 percent level.

III. THEORY

The short-term behavior of tracer albumin in the circulation of the rat can be described using a multiple compartment model (Figure 1). Immediately after injection, all the radioactive albumin is in the plasma compartment. It then begins to move into the other compartments that represent the interstitial fluid in various tissues. This movement occurs at a different rate for each tissue, depending on its characteristic PS. Eventually the albumin is returned to the circulation via the lymph.

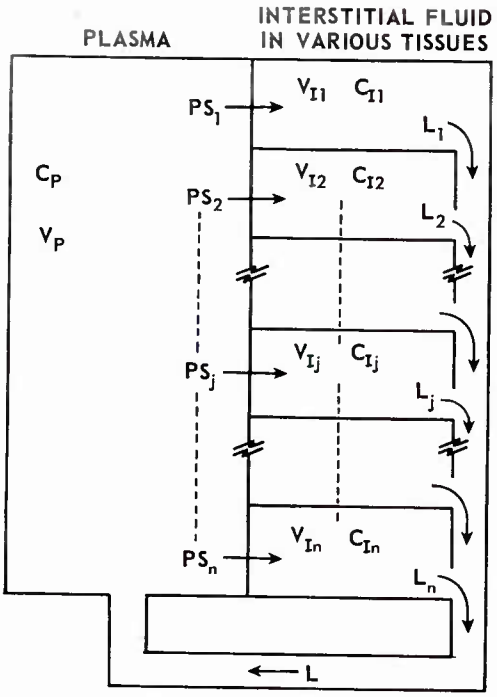

Figure 1. Model used to describe short-term behavior of radioactive iodinated albumin in the circulation of a rat.
C = concentration of radioactive albumin in the indicated compartment
V = volume of the indicated compartment
P = permeability of capillary walls (cm/min)
S = surface area of capillary walls available for exchange
L = lymph flow for the indicated compartment

It is assumed that the animal has an average capillary permeability area that determines the level of tracer albumin in the plasma, but that the permeabilities of the various tissues can differ. An average permeability for the whole animal seems reasonable since the disappearance curve for iodinated albumin in the circulation of the rat is a single exponential for the first few hours after injection.[14]

The differential equations describing the time course of the concentration of radioactive albumin in the plasma (C_p) and in the average interstitial fluid (C_I) are:

$$\frac{dC_p}{dt} = \frac{-PS(C_p - C_I) + L \cdot C_I}{V_p} \tag{1}$$

$$\frac{dC_I}{dt} = \frac{PS(C_p - C_I) - L \cdot C_I}{V_I} \quad . \tag{2}$$

L is the whole-body lymph flow, V_p is the plasma volume and V_I is the interstitial fluid volume. PS is the average capillary permeability surface area product for the entire animal in equations (1) and (2).

In a particular tissue (subscripted j) the pertinent equation is:

$$\frac{dC_{Ij}}{dt} = \frac{PS_j(C_p - C_{Ij}) - L_j \cdot C_{Ij}}{V_{Ij}} \quad . \tag{3}$$

By introducing the following three simplifying assumptions this relatively complex model becomes experimentally useful: (1) the concentration of tracer albumin in the plasma (C_p) remains relatively constant during the course of the experiment;[6] (2) the concentration of tracer albumin in the interstitial fluid (C_I) remains relatively low during the course of the experiment; and (3) lymph flow is negligible. These assumptions are justified later.

Equations (1), (2) and (3) now become:

$$\frac{dC_p}{dt} = 0 \tag{4}$$

Whole animal: $$\frac{dC_I}{dt} = \frac{PS \cdot C_p}{V_I} \tag{5}$$

Particular tissue: $$\frac{dC_{Ij}}{dt} = \frac{PS_j \cdot C_p}{V_{Ij}} \quad . \tag{6}$$

The solution for equation (6) is:

$$C_{Ij} = \frac{PS_j \cdot C_p \cdot t}{V_{Ij}} \quad . \tag{7}$$

In a particular sample of tissue there exists a given interstitial fluid volume (V_{Ij}) and a given residual intravascular plasma volume (V_{Rj}). The total activity (A) of a sample of tissue would then be:

$$A = V_{Ij} \cdot C_{Ij} + V_{Rj} \cdot C_p \tag{8}$$

$$A = PS_j \cdot C_p \cdot t + V_{Rj} \cdot C_p \quad . \tag{9}$$

Since the ^{131}I albumin circulates for 30 minutes and the ^{125}I albumin circulates for 10 minutes, two separate equations can be written dropping the individual tissue subscripts:

$$A^{131} = PS \cdot C_p{}^{131} \cdot 30 + V_R \cdot C_p{}^{131} \tag{10}$$

$$A^{125} = PS \cdot C_p{}^{125} \cdot 10 + V_R \cdot C_p{}^{125} \quad . \tag{11}$$

The solution for PS for a particular tissue sample, using the simplified model, is then

$$PS = \frac{1}{20}\left(\frac{A^{131}}{C_p{}^{131}} - \frac{A^{125}}{C_p{}^{125}}\right) \quad . \tag{12}$$

The simplified model was compared with the more complex model to estimate the inherent error introduced in the simplification. A computer program was written using equations (1), (2) and (3) as difference equations with a step increment of 1 minute. A total plasma volume of 3 percent of body weight and an interstitial fluid volume of 30 percent of body weight were used. Given various average and particular tissue permeability areas, residual plasma volumes and lymph flows, the program calculated the levels of tracer albumin at 10 and 30 minutes after injection. These values were substituted into equation (12) and PS was calculated. The ratio of calculated

tissue PS to given tissue PS is shown in Figure 2 for several values of the various variables. The range of these variables exceeds their range as reported in the literature[6,7] or as observed during the course of these experiments. Within this range the calculated values do not differ from the given values by more than 16 percent.

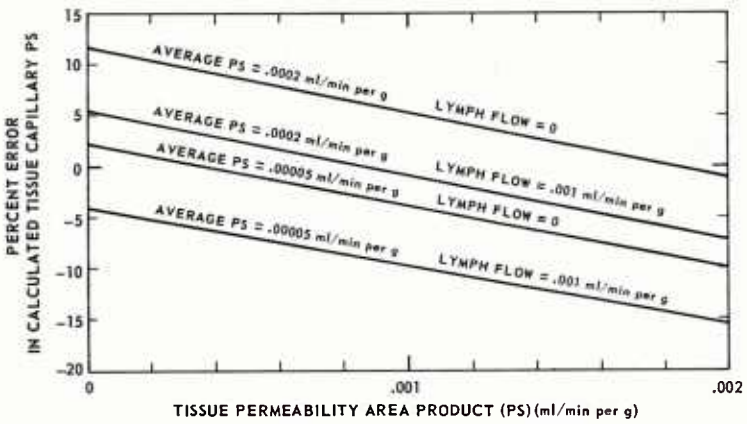

Figure 2. Inherent error in the simplification of the model. A relatively complete model was used to calculate the concentration of radioactive albumin in the plasma and in the tissues at 10 and 30 minutes after injection for the range of values indicated. The resulting data were used to calculate PS using an equation derived from the simplified model. The error indicated is the deviation from unity of the ratio of tissue capillary PS calculated using the simplified model to the PS used in the complete model. The ranges for the various variables exceed that expected or observed.

The residual plasma volume introduces no theoretical error but, because of the random nature of radioactive decay, is responsible for much of the experimental error in the procedure. In equation (12) we take the difference between two count ratios. If the difference is small, the error may represent an important fraction of the difference. For example, muscle PS is about one-sixth that of small intestine and the standard deviation for muscle PS is 85 percent of the mean while it is only 35 percent for small intestine. Both of these errors are greater than the 16 percent error expected because of the simplification of the model.

An additional source of error arises in the group of rats that were evaluated just after the 10,000-rad ^{60}Co exposure. During the course of the procedure, capillary permeability probably changed considerably and, since the calculation assumes steady state, the calculated PS was probably in considerable error. Because of this error the computation was primarily valuable for defining differences between groups rather than calculating absolute values for this group.

IV. RESULTS

The capillary permeability areas (PS's) were determined for small intestine and muscle between 1 and 216 hours (9 days) after 800 rads whole-body fast electron irradiation. The small intestine PS (Figure 3) increased significantly by 1 hour after irradiation, returned briefly to control levels at 2 through 4 hours, was again increased at 8 hours, and remained elevated for several days. Muscle PS (Figure 4) became significantly elevated by 2 hours after irradiation and remained elevated for several days.

In the second experiment the effect of cyproheptadine on postirradiation PS changes was examined (Figure 5). Cyproheptadine blocks the action of serotonin and

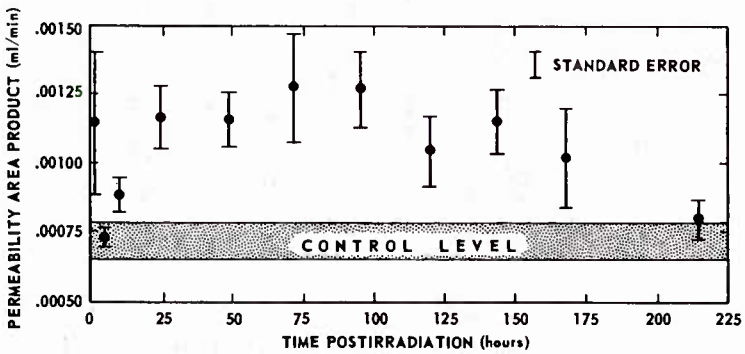

Figure 3. Capillary permeability area of rat small intestine following 800 rads fast electron irradiation. All points excepting the ones at 4, 168 and 216 hours are significantly above control.

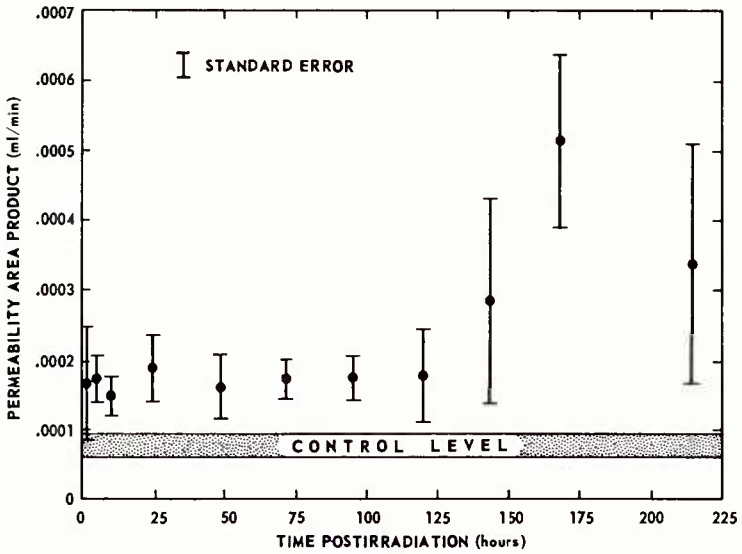

Figure 4. Capillary permeability area of rat muscle following 800 rads fast electron irradiation. All points excepting the ones at 1, 120, 144 and 216 hours are significantly above control.

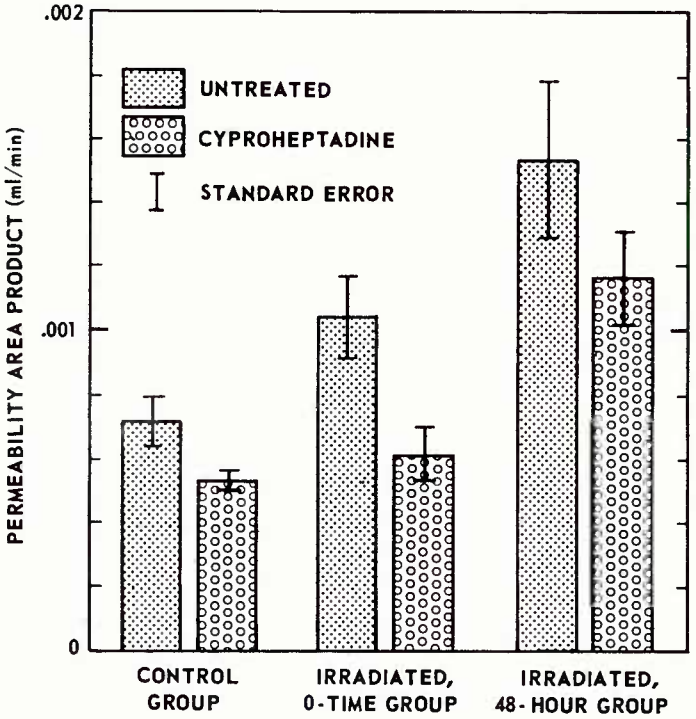

Figure 5. Capillary permeability surface area product of rat small intestine after 10,000 rads cobalt-60 irradiation. The treated groups were injected subcutaneously with 0.1 mg/kg cyproheptadine 30 minutes prior to the beginning of the measurement of the capillary permeability area.

histamine.[2,13] There was a small but significant decrease in small intestinal PS in the treated control animals. For the animals killed 30 minutes following exposure to 10,000 rads ^{60}Co irradiation, cyproheptadine completely prevented the increase in PS seen in untreated animals. Cyproheptadine significantly reduced but did not completely reverse the increase in PS seen in untreated animals 48 hours postirradiation.

V. DISCUSSION

Following 800 rads whole-body fast electron irradiation, the small intestine capillary permeability area was assessed by measuring the movement of radioactive iodinated albumin into tissue using a double isotope technique. It increased by 60 percent immediately after irradiation, returned to normal within a few hours, and then increased again and remained at about 65 percent above normal for several days. After day 6, the permeability area of surviving rats returned toward control levels which may reflect recovery from radiation damage. The biphasic behavior is in accord with the observations of Harris and Noonan,[3] who used the appearance of intravascularly injected radioactive albumin in the peritoneal fluid of rats to measure capillary permeability following irradiation.

The prolonged plateau in the small intestine capillary PS for several days after irradiation has not been previously reported. This plateau may indicate that the radiation damage, such as deterioration of the basement membrane[16] surrounding the capillaries, may manifest itself within a few days after irradiation and then remain relatively constant until it is repaired several days later. Alternatively there could be a progressive deterioration of the capillaries[16] leading to an increase in capillary permeability, but at the same time there may be a decrease in the area available for

exchange due to progressive vasoconstriction.[4] Thus the capillary permeability area could remain relatively constant for several days.

The data for muscle capillary PS following 800 rads electron irradiation are not explicit enough to draw any conclusions except that it is definitely elevated for several days after irradiation.

Both serotonin and histamine are contained in the mast cells in rats, and these cells discharge their granules containing these substances at the time of irradiation.[10] In rats, serotonin is more effective than histamine in increasing capillary permeability.[2] Cyproheptadine, a surmountable, competitive inhibitor of serotonin and histamine[2,13] caused a slight drop in the small intestine capillary permeability area in unirradiated animals. This would be consistent with the inhibition of circulating histamine or serotonin. Cyproheptadine completely blocked the 45 percent increase in small intestine capillary PS immediately following 10,000 rads, but was only slightly effective 48 hours later.

Other investigators have found antihistamines to be effective in blocking the increased capillary permeability at 24 hours after irradiation in the rabbit[8] and in the rat,[15] and ineffective at 90 minutes in the rabbit[5] and at 6 hours in the rat.[3] An antiserotonin was found to be ineffective in the rat when tested 24 hours after irradiation.[15]

If these experiments are comparable, then serotonin may be responsible for the initial increase in capillary permeability in the rat, histamine may account for the observed increase at 24 hours, and structural defects[16] or some other mechanism may cause the prolonged increase after 48 hours. Further work using standardized conditions should test this.

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Capillary permeability was measured using ^{131}I albumin and ^{125}I albumin to assay the movement of albumin out of the bloodstream into the interstitial fluid of small intestine and muscle of the irradiated rat. One hour after 800 rads 30 MeV electron whole-body irradiation, small intestine capillary permeability increased significantly, returned to normal levels in a few hours, and then after 8 hours increased and remained at 65 percent above control levels for several days. Muscle capillary permeability increased within 2 hours after irradiation and remained elevated for several days. Cyproheptadine, an antiserotonin-antihistamine, completely blocked a 45 percent increase in small intestine capillary permeability seen immediately after 10,000 rads ^{60}Co irradiation but had little effect at 48 hours after irradiation.

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